

since it was not entered in the CRF's as such. This study report could be looked at as the report of a complicated combination of at least three different studies, with changes in their entry and retreatment criteria with 4 different CRF's intertwined.

This report, as submitted, can not support any conclusion on safety or efficacy of Infasurf, except on that of the incidence of total mortality in both arms, which are consistent with those obtained in well controlled studies.

V. Integrated Summary of Safety

The safety database for Infasurf was generated by pooling 3 controlled studies submitted by the sponsor to the NDA: the two pivotal studies, 9101 SCT-P and 9101 SCT-T, comparing Infasurf to Exosurf, and the only other controlled study ISCT-92, where Infasurf was compared to Survanta. A total of 3,098 patients were studied, 1,554 received Infasurf and 1,544 received an active control drug (Exosurf=978, and Survanta=566 patients). The 4 non-controlled, open label studies submitted by the sponsor have been reviewed and discussed individually in the previous section. None of them add new information to the present discussion.

Since the population involved in these three studies differed significantly in some relevant variables, i.e., birth weight, gestational age, respiratory status at entry into the study, etc., for some variables the studies were pooled by indication: for the prophylaxis (or prevention), and for the treatment (or rescue) of RDS; and the variables were presented as such.

Prophylaxis studies: Study 9101 SCT-P and Study 9201 ISCT-92 prophylaxis arm; involved 1,310 patients;

Treatment studies: Study 9101 SCT-T and 9201 ISCT-92 treatment arm; involved 1,788 patients.

Besides some differences in the definition of some of the variables studied, and in the method used to collect and analyze some of the data, the studies were deemed sufficiently similar to be able to generate meaningful data when combined in this safety database. Maybe one of the more obvious differences between the two controlled studies was the method of administration of Infasurf. In the SCT-P and T, it was given following the Exosurf labeling instructions: given through a side port in two aliquots. The prophylaxis trial provided for retreatment up to a total of 3 doses, and the treatment trial

up to 2 total doses given 12 hours apart. In the ISCT-92, Infasurf was given following the Survanta labeling instructions: through a feeding tube inserted just about the tip of the endotracheal tube, in four aliquots. Both, the prophylaxis and the treatment arm, could retreat up to a total of 3 doses at least 6 hours apart.

Pooling of all treated patients, however, of both prophylaxis and treatment populations, was also done for some particular variables, in an effort to obtain better estimates of adverse event incidence. These analysis will also be presented.

Because of the nature of the disease studied, it will be difficult to strictly separate some safety issues from efficacy outcomes, i.e., mortality and common complications encountered in the population studied. Thus, this section will review mortality, complications of prematurity and adverse events during administration of the surfactant as they relate in this NDA to measurements of safety. In the efficacy section they will be referred to and analyzed from the efficacy standpoint, to answer the question of the effectiveness of Infasurf related to active controls.

1. Demographic Characteristics

A. Prophylaxis Population

A total of 1,310 patients entered in the two randomized, double blinded, and well controlled studies. Six hundred fifty five patients were exposed to Infasurf and 655 patients received an active control drug (Exosurf=422 patients, Survanta=233 patients). TABLE 1 shows some of the demographic characteristics of the prophylaxis population studied.

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TABLE 1. Demographic characteristics. -Prophylaxis population.

Parameter	Study 9101 SCT-P		Study 9201 ISCT-92 (Prophylaxis arm)	
	Infasurf	Exosurf	Infasurf	Survanta
Birth Weight (grams)				
N	431	422	224	233
Mean	895.7	899.8	886	878
Std. Dev.	236.0	241.9	234	238
Gestational Age (weeks)				
N				
Mean	431	422	224	233
Std. Dev.	26.5	26.5	26.3	26.3
	1.6	1.6	1.8	1.8
Sex (%)				
N	431	422	224	233
Males	222 (52)	236 (56)	117 (52)	113 (49)
Race (%)				
N	431	422	224	233
White	244 (57)	240 (57)	103 (46)	101 (43)
Apgar 1 minute				
N	429	420	224	233
Mean	4.5	4.4	4.2	4.1
Std. Dev.	2.3	2.4	2.4	2.3
Apgar 5 minute				
N	429	421	224	233
Mean	7.1	7.0	6.4	6.4
Std. Dev.	1.7	1.8	1.9	1.8

COMMENTS:

The patients included in the sample size of the prophylaxis trials present in general a balance in the demographic characteristics across the studies.

B. Treatment Population

A total of 1,788 patients entered in the two studies, 899 patients were exposed to Infasurf and 889 patients received and active control drug (Exosurf=556 patients, Survanta=333 patients). TABLE 2 shows some of the demographic characteristics of the treatment population studied.

TABLE 2. Demographic characteristics. - Treatment population

Parameter	Study 9101 SCT-T		Study 9201 ISCT-92 (Treatment arm)	
	Infasurf	Exosurf	Infasurf	Survanta
Birth Weight (grams)				
N	570	556	329	333
Mean	1648.2	1563.7	1171	1165
Std. Dev.	720.8	680.0	414	402
Gestational Age (wks)				
N	570	556	329	333
Mean	31.0	30.6	28.3	28.2
Std. Dev.	3.5	3.3	3.0	2.9
Sex (%)				
N	570	556	329	333
Males	327 (57)	347 (62)	189 (57)	191 (57)
Race (%)				
N	567	552	329	333
White	401 (71)	375 (68)	165 (50)	159 (48)
Apgar 1 minute				
N	559	543	329	333
Mean	5.5	5.3	4.3	4.2
Std. Dev.	2.4	2.6	2.4	2.5
Apgar 5 minute				
N	559	543	329	333
Mean	7.4	7.2	6.4	6.5
Std. Dev.	1.7	1.9	2.0	2.1
Respiratory status at entry (Mean \pm St. Dev.)				
N	570	556	329	333
FIO ₂	0.75 \pm 0.21	0.74 \pm 0.21	0.74 \pm 0.22	0.75 \pm 0.23
PO ₂	62.9 \pm 23.8	61.0 \pm 21.4	63 \pm 30	66 \pm 33
PCO ₂	41.6 \pm 9.1	42.2 \pm 9.7	44 \pm 13	43 \pm 11
a/A Ratio	0.14 \pm 0.05	0.14 \pm 0.05	0.15 \pm 0.06	0.15 \pm 0.07

COMMENTS

The treatment population in the ISCT-92 was younger and lighter than the population in study 9101 SCT-T (the entry criteria in study ISCT-92 required patients to be <2,000 g of birth weight to be eligible, study SCT-T did not make such restriction), with lower Apgar scores at 1 and 5 min. However, the respiratory status at entry, is comparable in both studies. The study entry criterion for presence of RDS was the same: a CXR diagnostic of RDS and a/A PO₂ \leq 0.22.

2. Mortality

Mortality was analyzed by cause as follows:

- ☛ RDS deaths - death primarily due to RDS and its complications, occurred at ≤ 14 days of age.
- ☛ Respiratory deaths - deaths due to respiratory causes other than RDS, and
- ☛ Total neonatal mortality - defined as all deaths, from any cause, that occurred during the hospital stay at 7 and 28 days, and to discharge.

TABLE 3 presents mortality analyzed by cause in the prophylaxis population, TABLE 4 presents the data in the treatment population. TABLE 5 presents the pooled data from all patients treated in the 3 controlled studies.

TABLE 3. Mortality by cause. - Prophylaxis populations.

Mortality by Cause	ITT Population (N=853)			ITT population (N=457)		
	Infasurf (N=431)	Exosurf (N=422)	p-Value	Infasurf (N=224)	Survanta (N=233)	p-Value
7 days	31 (7)	47 (11)	0.05	22 (10)	7 (3)	<0.01
28 days	52 (12)	68 (16)	0.1	26 (12)	15 (6)	0.07
Total Mortality (to Discharge)	77 (18)	82 (19)	0.56	40 (18)	25 (11)	0.03
Respiratory Mortality	15 (3)	18 (4)	0.6	14 (6)	9 (4)	0.29
RDS Mortality	7 (2)	23 (5)	0.004	10 (4)	0 (0)	<0.01
Survival to Discharge	354 (82)	340 (81)	0.56	184 (82)	208 (89)	0.03

COMMENTS

Infasurf treated patients had a statistically significantly lower incidence of RDS mortality and total mortality at 7 days when compared with Exosurf. The statistical significance was lost at 28 days and to discharge. In the ISCT-92 study, Survanta had statistically significantly lower incidence in total mortality at 7 days and to discharge, as well as in RDS mortality. Further discussion of the findings pertaining this variable and the explanation offered by the sponsor of an "unusual and unexpected survival rate of the <600 g population in the Survanta group, which drove the data to reach statistical significance" can be found in the section dedicated to the review of the ISCT-92 prophylaxis trial study. The improved survival found in the Survanta prophylaxis population can not be explained by an unbalance on any of the entry criteria or demographic characteristics. In fact, Survanta patients were lighter than their counterparts. The meaning and implication of these findings in the determination of overall safety of Infasurf need further internal discussion and will be presented to the Advisory Committee members for their recommendation.

TABLE 4. Mortality by cause. -Treatment populations.

Mortality by Cause	ITT Population (N=1126)			ITT population (N=662)		
	Infasurf (N=570)	Exosurf (N=556)	p-Value	Infasurf (N=329)	Survanta (N=333)	p-Value
7 days	34 (6)	34 (6)	0.91	36 (11)	34 (10)	0.80
28 days	47 (8)	58 (10)	0.21	50 (15)	45 (14)	0.58
Total Mortality (to Discharge)	52 (9)	69 (12)	0.07	63 (19)	58 (17)	0.62
Respiratory Mortality	9 (2)	16 (3)	0.16	23 (7)	16 (5)	0.25
RDS Mortality	23 (4)	23 (4)	1.00	20 (6)	26 (8)	0.45
Survival to Discharge	518 (91)	487 (88)	0.07	266 (81)	275 (83)	0.62

COMMENTS

The incidence of mortality was similar in all treatment groups by cause or age. There is a numerical trend favorable to Infasurf in total mortality to discharge related to Exosurf. In this study Survanta did not reach the spectacular difference in mortality found in the prophylaxis arm.

TABLE 5. Mortality . - Pooled populations.

Mortality by cause	ITT population (N= 3098)		
	Infasurf (N= 1554)	Exosurf (N= 978)	Survanta (N=566)
7 days	123 (8)	81 (8)	41 (7)
28 days	175 (11)	126 (13)	60 (11)
Total Mortality (to discharge)	232 (15)	151 (15)	83 (15)
Respiratory Mortality	61 (4)	34 (3)	25 (4)
RDS Mortality	60 (4)	46 (5)	26 (5)
Survival to Discharge	1322 (85)	827 (85)	483 (85)

COMMENTS

Mortality was similar across all treatment groups when analyzed by age and by cause of death, when all the treated patients of the 3 studies were combined. However, the question regarding the relevance of the difference in mortality found in a single, supportive, trial between Infasurf and Survanta in the total context of safety for Infasurf still remains open for discussion.

3. Causes of Mortality

The causes of neonatal death are presented in TABLE 6. It is a pool of the data of all the patients treated in the three controlled studies.

TABLE 6. Summary of causes of death for all treated patients in the controlled studies.

Cause of Death	Infasurf (N=1,554)	Exosurf (N=978)	Survanta (N=566)
RDS	60 (4)	46 (5)	26 (5)
Bacterial infection and septicemia	45 (3)	25 (3)	17 (3)
Chronic lung disease	19 (1)	14 (1)	9 (2)
Lung hypoplasia syndromes	8 (<1)	8 (1)	2 (<1)
Birth asphyxia and previable births	7 (<1)	3 (<1)	2 (<1)
Brain hemorrhage	23 (1)	16 (2)	4 (1)
Necrotizing enterocolitis	20 (1)	7 (1)	5 (1)
Congenital hydrops and/or ascites	3 (<1)	2 (<1)	0 (0)
Congenital heart disease	4 (<1)	1 (<1)	2 (<1)
Chromosomal abnormality syndromes	0 (0)	1 (<1)	0 (0)
Other congenital anomalies	1 (<1)	1 (<1)	0 (0)
Renal failure	12 (1)	7 (1)	5 (1)
Pulmonary hemorrhage	14 (1)	9 (1)	5 (1)
Hepatic failure	2 (<1)	2 (<1)	0 (0)
Pneumonia	4 (<1)	3 (<1)	2 (<1)
Other causes	10 (1)	6 (1)	4 (<1)
TOTAL	232 (15)	151 (15)	83 (15)

COMMENT

The frequency of the different causes of death is similar across the treatments. Their combined incidence is similar to those of the individual studies analyzed separately by indication (prophylaxis and treatment) and when SCT-P and SCT-T were analyzed together. The results were also similar to this one when the two arms of the ISCT-92 (Infasurf-Survanta) were analyzed together.

4. Complications of Prematurity

The most common serious complications reported in the study populations were reviewed in this section: Brain hemorrhages (intraventricular hemorrhages [IVH] and periventricular leukomalacia [PVL]), air leaks (pneumothoraces, and parenchymal interstitial emphysema [PIE]), patent ductus arteriosus [PDA], sepsis, retinopathy of prematurity [ROP], and necrotizing enterocolitis [NEC].

In TABLES 7 and 8, the complications of prematurity are presented by the individual prophylaxis and treatment populations. The Infasurf prophylaxis data represents the combined results of the two controlled prophylaxis trials (SCT-P and the prophylaxis arm of the ISCT-92) and the treatment data the combined results of SCT-T and the treatment arm of ISCT-92. In TABLE 9 the prophylaxis and the treatment populations have been pooled together by drug products for a more in depth review of the incidence of complications. However, the comparison of all complications of prematurity between the treatment groups is difficult in this case because of a lack of uniform criteria across the studies in the definition and the analysis of some of the terms, e.g., PDA required ultrasound verification in the ISCT-92 and the denominator included only the number of patients evaluated; in the 9101 SCT-P trial the denominator included total number of patients in the trial, this yielded a comparable increment in the percentage of diagnosis of PDA in the Infasurf and Survanta-treated population in the ISCT-92 study. For this reasons, only brain hemorrhages and air leaks, which presented similar definitions and methods of analysis, will be pooled together. The rest of the complications of prematurity were analyzed in the individual study reports. It is noteworthy to comment here that even when the frequency of the other complications of prematurity was similar in all the treatment groups in the ITT population, in a subset analysis of patients <700 grams of the prophylaxis trial (SCT-P, Infasurf-Exosurf), Infasurf treated patients had a statistically significant increase in post hemorrhagic hydrocephalus ($p < 0.05$) and sepsis ($p < 0.01$), when compared to Exosurf treated patients.

TABLE 7. Complications of Prematurity. - Prophylaxis Population.

Safety Parameter	Infasurf (N=655)	Exosurf (N=422)	Survanta (N=233)
IVH only ^a	244/641 (38)	147/411 (36)	71/227 (31)
PVL only ^a	19/641 (3)	19/411 (5)	3/227 (1)
IVH and PVL ^a	50/641 (8)	17/411 (4)	13/227 (6)
IVH, PVL or both ^a	313/641 (49)	183/411 (45)	87/227 (38)
IVH Grade I or II	206/294 (70)	112/164 (68)	73/84 (87)
IVH Grade III or IV	88/294 (30)	52/164 (32)	11/84 (13)
Air leaks (Overall):	76/655 (12)	79/422 (19)	24/233 (10)
Pneumothorax	44/655 (7)	36/422 (9)	14/233 (6)
Pulmonary interstitial emphysema	46/655 (7)	58/422 (14)	13/233 (6)

^a As determined at study site. The Survanta trial did not have a central reader.

COMMENTS

With respect to cerebral hemorrhages, the pool of Infasurf prophylaxis patients presented an increase incidence of IVH across the studies. Infasurf presented more severe IVH (grades III and IV) and the combination of IVH and/or PVL with respect to Survanta, and more IVH and PVL combined with respect to Exosurf. In the individual studies, only the combined occurrence of IVH and PVL was statistically significant in favor of Exosurf. Regarding air leaks, Infasurf showed less air leaks overall and less PIE than Exosurf. The incidence of air leaks were similar between Infasurf and Survanta in the prophylaxis population.

TABLE 8. Complications of Prematurity. - Treatment Population.

Safety Parameter	Infasurf (N=899)	Exosurf (N=556)	Survanta (N=333)
IVH only ^a	214/821 (26)	142/507 (28)	116/295 (39)
PVL only ^a	16/821 (2)	11/507 (2)	2/295 (1)
IVH and PVL ^a	41/821 (5)	12/507 (2)	17/295 (6)
IVH, PVL or both ^a	270/821 (33)	165/507 (33)	135/295 (46)
IVH Grade I or II	170/254 (67)	109/154 (71)	104/133 (78)
IVH Grade III, or IV	84/254 (33)	45/154 (29)	29/133 (22)
Air leaks (Overall):	130/899 (14)	137/556 (25)	59/533 (18)
Pneumothorax	64/899 (7)	66/556 (12)	34/533 (10)
Pulmonary interstitial emphysema	82/899 (9)	105/556 (10)	44/533 (13)

^a As determined at study site. The Survanta trial did not have a central reader.

COMMENT

In the pooled treatment population, more Infasurf patients presented with severe IVH (grades III and IV) than Survanta treated patients. Survanta patients presented more IVH, PVL or both than Infasurf, more likely because Survanta also had more cases of IVH alone than Infasurf or Exosurf. It is noteworthy that Survanta had more cases of mild IVH (grades I or II) than Infasurf. In relation to air leaks, Infasurf tended to have less air leaks overall than Exosurf and Survanta.

TABLE 9. Complications of prematurity. Pooled data of all treated patients.

Safety Parameter	Infasurf (N=1554)	Exosurf (N=978)	Survanta (N=566)
IVH only ^a	458/1462 (31)	289/918 (31)	187/522 (36)
PVL only ^a	35/1462 (2)	30/918 (3)	5/522 (1)
IVH and PVL ^a	91/1462 (6)	29/918 (3)	30/522 (6)
IVH, PVL or both ^a	584/1462 (40)	348/918 (38)	222/522 (43)
IVH Grade I or 2	376/1462 (26)	211/918 (24)	177/522 (31)
IVH Grade III or IV	172/1462 (12)	97/918 (11)	40/522 (7)
Air leaks (Overall):	206/1554 (13)	216/978 (22)	83/566 (15)
Pneumothorax	108/1554 (7)	102/978 (10)	48/566 (8)
Pulmonary interstitial emphysema	128/1554 (8)	163/978 (17)	57/566 (10)

^a As determined at study site. The Survanta trial did not have a central reader.

COMMENT

In this analysis, where all patients were pooled by surfactant received, irrespective of the indication, the differences in the incidence of brain hemorrhages are markedly buffered. A positive trend is noticed in favor of Infasurf in the incidence of air leaks and PIE, especially against Exosurf.

5. Adverse Events During The Administration of Surfactant.

As mentioned earlier in this section, the method of administration of the surfactants was different in the SCT trials (Infasurf-Exosurf) than in the ISCT-92 trial (Infasurf-Survanta).

SCT-P and SCT-T trials (Infasurf-Exosurf):

Dosage - Infasurf: 3 mL/Kg. (\approx 100 mg of phospholipids/Kg. of body weight).
Exosurf: 5 mL/Kg. body weight.

In the prophylaxis trial the surfactant could be given up to a total of 3 doses.

In the treatment trial, the surfactant could be repeated once. In both trials the minimum time interval between doses was 12 hours.

Administration - The total dose was given through a side-port adaptor connected to the endotracheal tube, in 2 aliquots. Each aliquot was given in small boluses over 1 - 2 minutes with the patient in the supine position, head midline. For the first prophylactic dose the patient was manually ventilated, and for all the treatment doses the patient was mechanically ventilated, while the surfactant was being instilled.

ISCT-92 (Infasurf-Survanta, prophylaxis and treatment arms):

Dosage - Infasurf: 4 mL/Kg. (The concentration of phospholipids was changed from the to-be-marketed product to provide 100 mg of phospholipids/Kg. of body weight).
Survanta: 4 mL/Kg. (100 mg of phospholipids/Kg. of body weight).

In both arms the surfactant could be given up to a total of 4 doses, at least 6 hours apart.

Administration - The total dose was given through a 5 French end-hole feeding tube inserted to the end of the endotracheal tube in 4 equal aliquots.

Each aliquot was given with the patient in 4 different positions. For the first dose the patient was manually ventilated, for the retreatment doses the patient was mechanically ventilated after each aliquot.

Due to the differences in the administration technique and in the events related, the summary of the adverse events reported during the administration of the surfactant on each trial are presented separately. TABLE 10 summarizes the adverse events reported in the SCT-P and SCT-T trials and TABLE 11 recounts the AE's from the two arms of the ISCT-92 trial.

TABLE 10. Adverse events during dosing. SCT-P and SCT-T populations

DOSING COMPLICATIONS	TREATED POPULATION (N=1979)	
	Infasurf (N=1001)	Exosurf (N=978)
Bradycardia	336 (34)	181 (18)*
Airway obstruction	385 (39)	214 (22)*
Reflux	208 (21)	209 (21)
Cyanosis	652 (65)	543 (56)
Reintubation	25 (3)	4 (<1)*
Manual ventilation	161 (16)	76 (8)*
Any	781 (78)	690 (71)*

*p<0.01

TABLE 11. Adverse events during dosing. ISCT-92 population

DOSING COMPLICATIONS	TREATED POPULATION (N=1119)	
	Infasurf (N=553)	Survanta (N=566)
Bradycardia	83(15)	87(16)
Airway obstruction	18(3)	5(1)*
Extubated	8(1)	5(1)
Δ SBP > 5 mmHg	57(10)	55(10)
Suctioned within 1 hr	37(7)	17(3)*
Any	138(25)	140(25)

*p<0.01 SBP= systolic blood pressure

COMMENT

Infasurf-treated patients presented a statistically significant increase in nearly all the adverse events reported during the administration of the surfactants in the SCT (Infasurf-Exosurf) trials. The data generated from the prophylaxis and treatment trials combined is similar with that obtained in each individual study. Patients in the Infasurf group developed statistically significantly more airway obstruction and bradycardia, and required more reintubations and manual ventilation than patients in the Exosurf group. Consistent with these findings are the results of the ISCT-92 trial, where Infasurf patients presented statistically significantly more airway obstruction and required more suctioning within one hour than Survanta patients. These adverse events were reported to be transient and without other sequelae derived from them.

6. REVIEWER'S COMMENTS ON INTEGRATED SUMMARY OF SAFETY

The highlights of the discussion on integrated safety were:

Mortality: - Infasurf was consistently the same or better than one of the controls and not consistently worse than another. When all the patients of the controlled studies were pooled, mortality was similar in all the treatment groups. On the other hand, the statistically significant higher mortality found in Infasurf in the prophylaxis arm of the ISCT-92 trial (Infasurf-Survanta) is of concern. Its impact in the determination of the overall safety of Infasurf would require further discussions. Of note is to say that the causes of death were similar in all the treatment groups.

Complications of prematurity: - All other complications besides brain hemorrhages and air leaks, had similar incidence in the ITT population of all treatment groups.

Air leaks: - Infasurf tended to have less patients with air leaks across all studies than controls, except in the prophylaxis arm of the ISCT-92, Infasurf-Survanta trial.

Brain hemorrhages: - Infasurf tended to have more incidence/more severe degrees of intracranial bleedings than the active control (Exosurf) in the pivotal studies. The same tendency can be seen when compared with Survanta, and when all patients were analyzed together.

Dosing complications: - Infasurf had consistently more adverse events during its administration than controls, with increased incidence of airway obstruction and suctioning within one hour of dosing in one trial, and increase incidence of airway obstruction, reintubation, bradycardia, and manual ventilation in the other two studies. The events were considered mild to moderate in nature.

In general, the data reviewed here identified some safety issues, like an increased

mortality of Infasurf patients in one of the supportive studies (the prophylaxis arm of ISCT-92 trial [Infasurf versus Survanta]), the increased incidence/severity of brain hemorrhages in general, and an increased incidence of "transient" adverse events during the administration of Infasurf, as of concern, and require to be addressed in the labeling, after further discussion by the Advisory committee members. However, considering the high morbi-mortality of the population studied, the questionable nature of the negative results vs. the benefits that Infasurf demonstrated to provide to the patients, the results of the trials indicate that Infasurf can be considered safe to be used in the prevention and treatment of RDS.

VI. Integrated Summary of Efficacy

The database of efficacy was generated mainly from the two pivotal studies, SCT-P and SCT-T, comparing Infasurf to Exosurf. The only other study submitted by the sponsor, considered adequate and well controlled, the ISCT-92, (Infasurf-Survanta), was also included. Additional data were provided from 4 other uncontrolled, non-randomized, open label studies and will not be discussed in this section. All the studies have been fully reviewed in previous sections. TABLE 1 and 2 summarizes the two pivotal studies.

TABLE 1. SCT-P study

Study Design # Sites	Treatment, Dose	Number patients Each Treatment	Gestational Age (GA) Mean \pm SD (weeks)
Phase III, multicenter, masked, parallel group, active controlled study. 10 study sites	Infasurf: 3 mL/kg of 35 mg/mL x 3 doses, 12 hours apart each.	<u>ITT</u> Infasurf - 431 Exosurf - 422	<u>ALL PATIENTS</u> Infasurf: GA: 26.5 \pm 1.6 RACE: Cauc %: 56.6 Other %: 43.4
	Exosurf: 5 mL/kg x 3 doses, 12 hours apart each.	<u>TBW</u> Infasurf - 250 Exosurf - 237	Exosurf: GA: 26.5 \pm 1.6 RACE: Cauc %: 56.9 Other %: 43.1

TABLE 2. SCT-T TRIAL

Study Design	Treatment, Dose	Number patients Each Treatment	Gestational Age (GA) Mean \pm SD (weeks)
Phase III, multicenter, masked, parallel group, active controlled study	Infasurf: 3 mL/kg of 35 mg/mL x 2 doses, 12 hours apart. Exosurf: 5 mL/kg x 2 doses, 12 hours apart	ITT Infasurf - 570 Exosurf - 556 TBW Infasurf - 190 Exosurf - 213	ALL PATIENTS Infasurf: GA: 31.0 \pm 3.5 RACE: Cauc %: 70.7 Other %: 29.3 Exosurf: GA: 30.6 \pm 3.3 RACE: Cauc %: 67.9 Other %: 32.1

These two pivotal studies were reviewed and discussed in detailed in a previous section. The major highlights of those discussions are presented below.

In the SCT-P (Prophylaxis trial), there were no between treatment group differences in surfactant administration variables including mean age at first dose (13.1 minutes for Infasurf, 15.8 minutes for Exosurf), duration of dosing (7.5 minutes for Infasurf, 7.8 minutes for Exosurf), and number of prophylactic doses received (2.6 for Infasurf, 2.7 for Exosurf).

In the SCT-T (Treatment trial), there were no between treatment group differences with respect to surfactant administration variables including: patient age at time of first surfactant dose (approximately 12 hours for the ITT populations and 7.5 hours for the TBW populations), duration of dose (approximately 13 minutes for both the ITT and TBW populations), and mean number of doses received (approximately 1.9 for both the ITT and TBW populations).

A. Primary Efficacy Variables

The primary variables of efficacy for the pivotal studies discussed in this section were: incidence of RDS (for the Prophylaxis study), incidence of bronchopulmonary dysplasia (BPD), mortality due to RDS (for both trials), and air leaks (for the Treatment trial). TABLE 3 shows the results of each variable by treatment group in the prophylaxis trial. TABLE 4 shows the results in the treatment trial.

B. Secondary Variables

Secondary variables of efficacy were: severity of RDS, total mortality, incidence of crossovers, total respiratory mortality, respiratory support required at 28 days.

TABLE 3. Efficacy parameters. - Prophylaxis trial.

Parameter	ITT Population			TBW Population (700-1100 g)		
	Infasurf [N=431]	Exosurf [N=422]	p-Value	Infasurf [N=250]	Exosurf [N=237]	p-Value
RDS ¹	62/406 (15.3%)	183/389 (47.0%)	<0.001	36/233 (15.5%)	97/221 (43.9%)	<0.001
BPD ^{1a}	61/376 (16.2)	62/354 (17.5)	0.6	42/234 (17.9)	35/208 (16.8)	0.95
RDS Death ²	7 (1.6)	23 (5.5)	0.004	0 (0.0)	8 (3.4)	< 0.01
Mortality to 7 days ^b	31 (7.2)	47 (11.1)	0.05	8 (3.2)	19 (8.0)	0.04
28 days ^b	52 (12.1)	68 (16.1)	0.10	15 (6.0)	29 (12.2)	0.03
At Discharge: Survival	354 (82.1)	340 (80.6)	0.56	222 (88.8)	203 (85.7)	0.27
Mortality ^b	77 (17.9)	82 (19.4)	0.56	28 (11.2)	34 (14.3)	0.27
Any Air Leak	42 (9.7)	65 (15.4)	0.01	22 (8.8)	34 (14.3)	0.05
Pneumothorax	23 (5.3)	30 (7.1)	0.29	11 (4.4)	18 (7.6)	0.13
PIE	23 (5.3)	52 (12.3)	<0.001	15 (6.0)	26 (11.0)	0.04

¹ The 95% Confidence Interval for difference between treatment group percents was 31.7 ± 6.1 (ITT) and 28.4 ± 8.0 (TBW Population)

² the 95% Confidence Intervals for differences between treatment group percents were 3.9 ± 2.5 (ITT Population) and 3.4 ± 2.3 (TBW Population)

^bAny cause

[†] Denominators indicate survivors

TABLE 4. Efficacy variables. - Treatment Trial.

Parameter	ITT Population			TBW Population (700-1350 g)		
	Infasurf [N=570]	Exosurf [N=556]	p-Value	Infasurf [N=190]	Exosurf [N=213]	p-Value
BPD ^a	25/523 (4.8)	30/496 (6.0)	0.41	20/168 (11.9)	16/180 (8.9)	0.38
RDS Death [†]	23 (4.0)	23 (4.1)	0.95	14 (7.4)	16 (7.5)	0.95
Mortality to 7 days ^b	34 (6.0)	34 (6.1)	0.91	17 (8.9)	21 (9.9)	0.82
28 days ^b	47 (8.3)	58 (10.4)	0.21	22 (11.6)	33 (15.5)	0.32
At Discharge: Survival	518 (90.9)	487 (87.6)	0.07	163 (5.8)	171 (80.3)	0.17
Mortality ^b	52 (9.1)	69 (12.4)	0.07	27 (14.2)	42 (19.7)	0.17
Any Air Leak [*]	60 (10.5)	120 (21.6)	<0.001	28 (14.7)	71 (33.3)	<0.001
Pneumothorax	29 (5.1)	57 (10.3)	0.001	12 (6.3)	32 (15.0)	<0.01
PIE	39 (6.8)	94 (16.9)	<0.001	19 (10.0)	56 (26.3)	<0.001

^{*}The 95% Confidence Interval for difference between treatment group percents was 0.1 ± 2.3 (ITT Population) and 0.1 ± 5.1 (TBW Population)

[†]Denominators indicate survivors with data

^bAny cause

1. Incidence of RDS

Incidence of RDS was considered a measurement of efficacy in the prophylaxis trial, conducted in a population considered at high risk of developing respiratory distress syndrome. Its definition included a CXR positive for RDS (reticulo-granular infiltrates with or without air bronchograms), and an $\text{FiO}_2 \geq 30\%$ necessary to maintain the $\text{PaO}_2 > 50$ torr or pulse oximetry $> 85\%$ at the time of the CXR (16 to 36 hours).

The SCT-P, indicated that Infasurf was superior to Exosurf ($p < 0.001$) in the prevention of RDS.

In the ISCT-92, (Infasurf-Survanta) prophylaxis arm, there was no statistically significant difference between Infasurf and Survanta ($p = 0.55$).

2. Incidence of BPD

Chronic lung disease at 28 days was a primary endpoint in the prophylaxis and the treatment trials. Its definition included oxygen dependence and the Edwards-Toce Xray Score ≥ 4 on day 28.

The incidence of BPD was similar in all treatment groups of either study.

BPD is a parameter that has not been consistently effected by any surfactant treatment yet.

3. Mortality due to RDS

Mortality due to RDS was a primary efficacy endpoint in both, the prophylaxis and the treatment trials. It was defined as death, primarily due to RDS or to the complications of RDS (pneumothorax, air leaks, etc.), that occurred at or before 14 days (not associated with culture positive sepsis/pneumonia or with pulmonary hypoplasia).

In the prophylaxis trial (SCT-P), RDS death was statistically significantly lower in Infasurf patients than in the Exosurf group ($p=0.004$). In the treatment trial, (SCT-T) the incidence of RDS death was similar in both groups ($p=0.95$).

The pivotal studies showed that Infasurf was at least as effective as Exosurf in decreasing neonatal mortality due to RDS.

The ISCT-92 trial, prophylaxis arm, showed a statistically significant difference in RDS death in favor of Survanta ($p<0.01$), the treatment arm did not show a statistically significant difference in this endpoint between Infasurf and Survanta ($p=0.45$).

4. Incidence of RDS-related Air Leaks

These included pneumothorax and parenchymal Interstitial emphysema (PIE). This was a primary endpoint of the treatment trial.

Their incidence was analyzed based upon CXR's read at the sites and by a central radiologist reader (RRC). Even though they were numerically different, in both cases (when read at the sites and by the RRC), Infasurf-treated patients had statistically significantly less air leaks than Exosurf in both SCT trials:

In the prophylaxis trial, Infasurf had statistically significantly less air leaks in general ($p=0.01$) and less PIE ($p<0.001$) than Exosurf. In the treatment trial, Infasurf-treated patients had statistically significantly less air leaks (<0.001), pneumothoraces ($p=0.001$), and PIE ($p<0.001$) than the Exosurf-treated group.

The pivotal trials showed enough evidence to support that Infasurf was superior to Exosurf in decreasing the incidence of RDS-related air leaks.

In the ISCT-92 prophylaxis arm, there were no statistically significant differences in air leaks between Infasurf and Survanta.

5. Total Mortality

Neonatal mortality of any cause was a secondary endpoint in both trials. It was evaluated at 7 and 28 days and at discharge.

At 7 days: In the prophylaxis trial Infasurf had statistically significantly less mortality than Exosurf ($p=0.05$). In the treatment trial, the difference was not statistically significant. At 28 days and to discharge: There were no statistically significant differences in either SCT trial between Exosurf and Infasurf.

The pivotal studies showed that Infasurf was at least as effective as Exosurf in improving neonatal mortality.

In the ISCT-92 trial, in the prophylaxis arm, mortality was statistically significantly lower in the Survanta treated group at 7 days ($p<0.01$) and to discharge ($p=0.03$). In the treatment arm, there were no statistically significant differences between both treatment groups.

6. REVIEWER'S COMMENTS ON INTEGRATED SUMMARY OF EFFICACY.

Efficacy is a matter of comparison of the outcome or effect of a new drug to that of a placebo, or, in some cases, to a second active drug already approved for that indication. The results of the comparison show if the new drug is better, same or worse than the control. The sponsors seeking approval of new drugs for indication of disease states with a high risk of serious morbidity or mortality, can not use a placebo as the comparator of efficacy when there is already an approved drug for that indication in the market. In these cases, the sponsor has to prove that it is more effective than, or at least as effective as, the approved drug, for a clinically relevant variable, where the active control has consistently shown (in adequate and well controlled studies), to be better than placebo. The population should be similar to the target population for the new drug. The sponsor planned to demonstrate that Infasurf is superior to Exosurf, a synthetic surfactant approved for the prevention and treatment of RDS.

Infasurf showed superiority to Exosurf in the pivotal study SCT-P (the prophylaxis study) in clinically relevant variables such as incidence of RDS, RDS deaths, total mortality at 7 days, and in the incidence of air leaks. In the second pivotal study, SCT-T (the treatment trial) Infasurf showed superiority in air leaks, and was comparable to Exosurf in all the other parameters.

Compared to the second surfactant already approved in the market, Survanta, Infasurf demonstrated statistically significant increase in the incidence of total mortality and mortality due to RDS in the prophylaxis trial. As discussed before (pages 84 - 86), the reason of the increased mortality in a single supportive trial is not completely clear to this reviewer and should be viewed with caution, possibly as an isolated event, especially because it failed to show reproducibility. The mortality results were similar in the treatment arm of the same trial.

7. CONCLUSION

From the above data we can conclude that the pivotal studies support the efficacy and safety of Infasurf for the prevention and treatment of Respiratory Distress Syndrome.

Further discussions with the Advisory Committee may elucidate the impact that the increased mortality found in Infasurf-treated patients in the prophylaxis arm of a supportive study (Infasurf - Survanta) should have in the labeling. Besides the difference in mortality, Infasurf and Survanta had comparable results in all the other clinically relevant parameters.

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05/22/96

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05/22/96

Concurrence by Deputy Director/Supervisor:

Yes _____ No _____

Signature/Date *noted.* on 5/22/96
Comments: *see Supervisory NDA memo.*

Concurrence by Team Leader:

Yes ✓ No _____

Signature/Date 5/22/96
Comments:

Concurrence by Division Director:

Yes _____ No: Noted.

Signature/Date 6/24/96
Comments:

*see Division Director's
memo*

Concurrence by Division Director:

Yes ✓ No: _____

Signature/Date 5/24/96
Comments: